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EPILEPSY AND CROHN'S DISEASE

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ABSTRACT:

Background: Seizures are described in Crohn's disease. The etiology of these seizures is unclear but is thought to be related to inflammatory or hypercoagulable mechanisms. We have found a group of patients with both epilepsy and Crohn's disease, without significant abnormalities on imaging, raising the possibility of a genetic link. A genetic etiology has been described in Crohn's disease, specifically in relation to IBD 1 (NOD2) gene. Many genetic defects have also been found to increase susceptibility to seizures. We explored these cases to find support for a possible genetic link between seizures and Crohn's disease.

Methods: Case series/Literature review.

Case descriptions: Four patients of the 150 patients in our epilepsy clinic were identified with Crohn's disease, a much higher prevalence than would be expected from population prevalence of the disease. The case presentations of these patients are described, as well as an additional patient not affected by Crohn's but with a strong family history of the condition. The patients' family histories are explored. All of our patients have positive family histories of either seizures or Crohn's disease. Two of the patients have family histories both of seizures and Crohn's disease.

Conclusion: Genetic associations have been described for both seizures and Crohn's disease. Coexistence of two genetically transmitted diseases, such as Crohn's disease and epilepsy, can help in chromosomal and genetic localization. Our case series raises the possibility of this association and can serve as a nidus for future research.

BACKGROUND

An increasing number of links have recently been found between neurological diseases and inflammatory bowel diseases, including Crohn's disease. Neurological manifestations are seen in anywhere between 0.2-35.7% of patients with Crohn's disease, and are mainly related to cerebrovascular disease. Epilepsy has been quoted to be responsible for 15-50% of the neurological involvement in Crohn's disease patients.^{1,2} The underlying process for the seizures and epilepsy is thought to be related to inflammatory or hypercoagulable mechanisms, but this is not well understood.² Recently, a genetic basis has been discovered for Crohn's disease. Numerous genetic etiologies have also been found in relation to seizures and epilepsy. Because both disorders have known genetic etiologies, the possibility exists that a common genetic link may exist. We reviewed one hundred fifty consecutive charts from our adult epilepsy clinic at the University of Alberta Hospital, to identify patients with Crohn's disease,

and analyzed these patients' family history for the presence of Crohn's disease or epilepsy.

CASE DESCRIPTIONS

Of the one hundred and fifty patients in our epilepsy clinic, four patients were found with Crohn's disease. The population prevalence of Crohn's disease has been estimated between 26 to 198.5 per 100,000 individuals, with Canadian data at the higher end of this estimate.^{3,4} Thus, the prevalence within our epilepsy clinic is higher than what would be expected based on the population prevalence. We also included another patient without Crohn's disease, but with a pronounced family history of both Crohn's disease and seizures.

Case 1: A fifty-four year old right-handed woman with seizures since age nineteen. She described these events as brief periods of altered consciousness. Each episode

would only last for a second. She denied ever having lost consciousness, but had bitten her tongue while asleep. She had briefly been treated with phenytoin when she was nineteen, but was unable to tolerate the medication. She recalled that when she was a teenager, her teachers told her that she was frequently "daydreaming". The patient's past medical history was remarkable for Crohn's disease. The patient's son also suffered from seizures, beginning when he was 18 months old. Her son also had Crohn's disease. Two of her nieces had also had problems with seizures.

The patient's magnetic resonance imaging (MRI) scan was unremarkable. Her electroencephalogram (EEG) revealed generalized epileptiform discharges in a bifrontal distribution. She was diagnosed with idiopathic generalized epilepsy and started on valproic acid.

Case 2: A thirty-five year old right-handed man with newly diagnosed seizures. The patient had returned home from work unable to recall the day's events, and that evening had a witnessed generalized tonic-clonic seizure. The patient had been diagnosed with Crohn's disease ten years previously, treated with a bowel resection. He also carried diagnoses of asthma and psoriasis. The patient's family history includes two maternal great-uncles with epilepsy and his father also has psoriasis. The patient's MRI was unremarkable. His EEG showed right temporal slowing and sharp waves. He was diagnosed with localization related epilepsy, and is being managed with carbamazepine.

Case 3: A thirty-one year old right-handed man with a history of seizures since age fourteen. The patient described two types of seizures. His "mild episodes" would last for about thirty seconds, in which he would stare, swallow, and pick up objects. The patient would also have generalized tonic-clonic seizures, and had been hospitalized with status epilepticus on one occasion. The patient also had Crohn's disease. His past history was otherwise unremarkable. The patient had a brother with both Crohn's disease and psoriasis. He also had two maternal aunts who were also diagnosed with Crohn's disease. He also had a second cousin with seizures, and another second cousin with Crohn's disease. The MRI was unremarkable. He had multiple EEG's, demonstrating epileptic discharges in both temporal regions. A single photon emission computed tomography (SPECT) scan showed increased cortical perfusion in the anterior inferior frontal cortex. Because of no demonstrable lesion on MRI, it was decided he should continue with medical therapy.

Case 4: A thirty-four year old right-handed woman who had been recently diagnosed with seizures. The episodes came with little warning, involving loss of consciousness

with generalized tonic-clonic seizures and loss of bladder control. The patient was briefly cyanotic at birth, was slightly developmentally delayed and required special education classes. The patient had no family history of seizures, but her mother, brother, maternal grandmother, and maternal aunt had all been diagnosed with Crohn's disease. The patient's MRI revealed mild white matter loss. Her EEG showed a single burst of bifrontal activity. She was diagnosed with localization related epilepsy, and was treated with carbamazepine.

Case 5: A thirty-two year old right-handed man who had seizures since the age of twelve. The patient reported having several "small seizures" as well as generalized tonic-clonic seizures. He described his seizures as occurring with an aura including déjà vu and an epigastric sensation, and would then stare into space. He was able to speak during seizures. Most often his seizures occurred on awakening. Sleep deprivation would lead to more seizures. The seizures were being treated with valproic acid and topiramate. The patient's past medical history included psoriasis as well as mild cyanosis at birth, but no known birth injury. The patient's family history was interesting. He had a sister who suffered seizures as a child until the age of 5. His father and many paternal uncles had been diagnosed with Crohn's disease. The patient's physical examination was unremarkable. No intracerebral lesions were seen on MRI. EEG revealed epileptiform activity in the left temporal region.

DISCUSSION

Recently, a lot of work has been done on the genetics of inflammatory bowel disease, especially Crohn's disease. Multiple gene loci have been identified. The most studied has been the IBD1 locus, identified first by Hugot et al. in 1996.⁵ This gene locus has specifically been associated with Crohn's disease. It is located on chromosome 16q21, and contains the NOD2/caspase-activation recruitment domains 15 (CARD15) gene. This gene is expressed in peripheral blood monocytes and is thought to be involved in host resistance to microbial pathogens. The three major polymorphisms associated with Crohn's disease (Arg702Trp, Gly908Arg, and Leu1007fsinsC) are located in the portion of the gene that encodes for the pattern-recognition receptor, which recognizes many types of microbial components, including bacterial lipopolysaccharides.⁶ Having one copy of the abnormal allele increases the patient's risk of Crohn's disease two to four fold, and having two abnormal alleles increases the risk twenty to forty fold.⁶ The IBD2 locus has been identified on chromosome 12q13, but it has been only inconsistently replicated, and its gene product has yet to be identified.⁷ The IBD3 locus on chromosome 6p13 likely

encodes for major histocompatibility complex, and allelic foci have been found within this locus in relation to both Crohn's disease and ulcerative colitis. The specific gene involved has been difficult to find, as with other diseases with a HLA component.⁷ Other important genes appear to be in this region. The tumor necrosis factor (TNF) gene is also located in this region⁶, and has been linked to both Crohn's disease as well as other inflammatory conditions. Interesting and relevant to epilepsy, a genetic defect in patients with juvenile myoclonic epilepsy has also been studied near this gene locus, on chromosome 6p11-12, called EJM1.⁸ Many other gene loci are also under investigation, and results look promising to finding even more related genetic defects.

Genetic loci have also been found in relation to seizures and epilepsy. More than seventy gene loci have already been identified.⁹ Broadly, these can be classified into symptomatic epilepsies, in which an underlying structural defect can be identified, and idiopathic epilepsies, where no defect can be found. Multiple and diverse genetic defects have been found in the first group, ranging from progressive myoclonic epilepsies such as Lafora body disease and the EPM2 gene, to neuronal migration disorders such as subcortical band heterotopia and the DCX gene. In contrast, the majority of genetic defects in the idiopathic epilepsies relate to channelopathies.^{9,10} However, the discovered genetic influences to date only make up a small group of the familial epilepsies, and the remainder appears to have a more complex non-Mendelian inheritance.

Common links between disorders has become important in determining responsible genetic defects. Recently, a lot of interest has been generated surrounding a possible genetic link between psoriasis and Crohn's disease. Crohn's disease patients have approximately a 7-fold increase chance of also developing psoriasis.¹¹ This raised the possibility of a genetic linkage between the two conditions, especially in relation to the IBD1 gene locus. Unfortunately, a large linkage study found no association between the two conditions for the Leu1007fsinsC variant.¹² However, more studies searching for other allelic variants will have to be performed before ruling out a link. In addition, tumor necrosis factor has been found to have a significant role in both conditions, and a common genetic defect in this gene may also be significant, especially for therapeutic implications.¹³

A similar connection may be found between Crohn's disease and epilepsy. Currently, many neurological disorders have been linked to Crohn's disease, mainly on inflammatory or hypercoagulable mechanisms.² These disorders include cerebrovascular disease, myelopathy, peripheral neuropathy, and a multiple sclerosis-like

syndrome.¹⁴ Seizures and epilepsy have also been linked on these grounds, but our group of patients raises an interesting possibility of a genetic link between the two conditions outside of these mechanisms. Determining a connection would not only link the two conditions allowing a better understanding of the underlying pathophysiological mechanisms, but may also have therapeutic implications, as is the case with Crohn's disease and psoriasis and the use of infliximab, a monoclonal antibody directed against tumor necrosis factor alpha.¹⁵

CONCLUSION

This case series provides an anecdotal and potential relationship between epilepsy and Crohn's disease. Seizures noted in patients with Crohn's disease are usually attributed to cerebrovascular accidents, and we did not come across any published data exploring or even questioning a possible genetic link between these two conditions. In our epilepsy clinic, there are definitely an increased number of patients with Crohn's disease than would be expected from its population prevalence. It is also interesting that in all the patients we identified, some evidence of a family history of seizures or Crohn's disease is also found. All these patients underwent investigation with MRI. In light of the normal imaging, we are suspicious of a possible genetic link between these two conditions.

Whatever the case, this area should provide exciting research in the future. We plan to work with our inflammatory bowel diseases' clinic to study the prevalence of seizures in patients with Crohn's disease.

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